

IN THE SPECIFICATION

Please amend the specification as follows, wherein changes in a paragraph are shown by strikethrough or double brackets for deleted matter and underlining for added matter.

Page 1, please delete the paragraph beginning on line 25, and replace with the following paragraph:

The receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. Approximately[[,]] 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily is comprised of EGFR, HER2, HER3, and HER4. Ligands of this subfamily of receptors include epithelial growth factor, TGF- α , amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF- α and β receptors, CSFIR, c-kit and FLK-II. The FLK family is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1) (Plowman et al., DN&P 7(6):334-339, 1994, which is hereby incorporated by reference).

Page 2, please delete the paragraph beginning on line 12, and replace with the following paragraph:

Both receptor-type and non-receptor type tyrosine kinases are implicated in cellular signaling ~~signaling~~ pathways leading to numerous pathogenic conditions, including a variety of cancers. For example, the Bcr-Abl tyrosine kinase is the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). Inappropriate Bcr-Abl activity is also demonstrated in murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Page 2, please delete the paragraph beginning on line 19, and replace with the following paragraph:

Drug screening has been used *in vitro* to try and identify new compounds with potential cell line-specific anti-tumor ~~tumour~~ activity. Such a screening was published with respect to the compound N,N'-bis[4-(1,4,5,6-tetrahydro-5-methyl-2-pyrimidinyl)phenyl]- 2,5-pyridinedicarboxamide dihydrochloride (also known as 4'4''-bis(1,4,5,6-tetrahydro-5-methyl-2-pyrimidinyl)- 2,5-pyridinedicarboxanilide dihydrochloride trihydrate) (National Cancer Institute 1965)₁ which was not identified as a protein tyrosine kinase inhibitor. The screening₁ conducted using a leukemia mouse model₁ was not conclusive.

Page 3, please delete the paragraph beginning on line 3, and replace with the following paragraph:

The present invention relates to the identification of the role of COTI-001 to inhibit, regulate and/or modulate tyrosine kinase signal transduction to treat tyrosine kinase-dependent diseases and conditions, such as cancer and tumor ~~tumour~~ growth, and the like in mammals.

Page 17, please delete the paragraph beginning on line 14, and replace with the following paragraph:

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention₁ which contain a basic or acidic moiety₁ by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Page 21, please delete the paragraph beginning on line 24, and replace with the following paragraph:

For oral use of a chemotherapeutic compound selected from the group consisting of Formula I and/or II, a pharmaceutically acceptable salt thereof, a stereoisomer thereof, and mixtures thereof, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers that ~~which~~ are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

Page 27, please delete the paragraph beginning on line 21, and replace with the following paragraph:

Molecules with the potential target biological activity were analyzed in a validated *in silico* assay that is based on public domain National Cancer Institute *in vitro* anti-cancer data. The molecules are first decomposed to 110 descriptors using a proprietary CHEMSASTM algorithm. This decomposition process results in ~~is~~ a molecular data pattern of 110 variables that is then input into the *in silico* model. The output of the model is a prediction of the -Log(GI50) for the molecule(s) being analyzed against the specific cancer cell type in question i.e. breast cancer or leukemia, etc. A specific *in silico* assay was also developed for the leukemia cell line (i.e. K562) that over expresses the abnormal protein

tyrosine kinase found in chronic myelogenous leukemia (CML) and P388 murine acute myelogenous leukemia (ALL). Results of the *in silico* assay for molecular Formulas I and II in a number of cancer cell types are summarized below in Table 1.